

Peripheral Calcifying Epithelial Odontogenic Tumor Associated With Generalized Drug-Induced Gingival Growth: A Case Report

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Calcifying epithelial odontogenic tumor (CEOT) or Pindborg tumor is a rare, benign neoplasm of odontogenic origin, which accounts for about 0.4% to 3% of all odontogenic tumors.^{1,2} This lesion was described as a distinct entity for the first time by Pindborg in 1955 and was designated as Pindborg tumor in 1967.^{3,4} Intraosseous location of the tumor is the most common, accounting for about 94% of the cases reported thus far, but an extraosseous or peripheral variant was also described by Pindborg in 1966 and corresponds to approximately 6% of all cases of CEOT.^{3,5,6}

Clinically, peripheral CEOT appears as an asymptomatic lesion of firm consistency in the anterior gingiva, which may or may not show an ulcerated surface due to secondary trauma, and might be confused with fibrous hyperplasia, pyogenic granuloma, or peripheral giant cell lesion. Because this variant is extremely rare, its incidence and prevalence are still unknown, although the few cases reported in the literature indicate a discrete predominance in men with a mean age of 34.4 years.^{1,7}

The treatment of choice for CEOT ranges from simple enucleation to radical resection in some cases of invasive intraosseous CEOT. We present here an unusual case of peripheral CEOT associated with generalized drug-induced gingival growth in an 18-year-old patient, and discuss the main aspects of this very rare variant reported in the literature.

Report of a Case

Patient E.L.S., an 18-year-old man with melanoderma, was seen at the Discipline of Periodontics, Universidade Potiguar, with complaints of generalized gingival growth. The medical history showed that the patient had mental disease and epilepsy, had been using gardenal (phenobarbital, 100 mg/day) and hydantal (phenytoin, 100 mg/day) for about 10 years, and was currently treated with tegretol (carbamazepine, 200 mg/day). Intraoral clinical examination showed asymptomatic, hyperplastic, generalized gingival growth of fibrous consistency with a pale pink color and bleeding upon probing, as well as numerous deposits of dental biofilm and dental calculus. The buccal surfaces of the anterior teeth were more affected, mainly in the papillae, partially covering the teeth and forming pseudopockets (Figs 1, 2). The patient also presented a lesion clinically diagnosed as pyogenic granuloma that filled a caries lesion located in the lower right first molar (Fig 3). Radiographic examination showed no signs of periodontitis. Based

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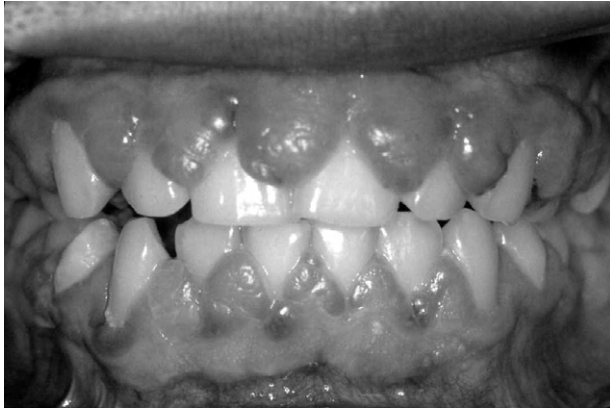


FIGURE 1. Facial view of the anterior teeth showing evident gingival overgrowth.

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on these findings, a clinical diagnosis of drug-induced gingival growth was made.

Treatment was then initiated that consisted of basic procedures for the removal and control of the biofilm and dental calculus, including scaling and crown planing and oral hygiene instructions. In addition, conventional gingivoplasty in the anterior areas and internal bevel gingivoplasty in the posterior areas were performed in various steps. The surgical specimens were sent to the Pathological Anatomy Service of the Discipline of Oral Pathology, Universidade Federal do Rio Grande do Norte, where they were processed and stained with hematoxylin and eosin. Light microscopy analysis of the anterior areas of the maxilla and mandible, as well as of the posterior areas of the maxilla and left side of the mandible showed histopathological data compatible with drug-induced gingival growth. However, in the case of the lesion located in the region of the lower right first molar with a clinical diagnosis of pyogenic granuloma, the histological sections showed fragments of a benign neoplasm of odontogenic origin characterized by the proliferation of hyperpigmented epithelial cells arranged in islets and chains and foci of basophilic material resembling dystrophic calcifications, some of them exhibiting concentric arrangements characteristic of Liesegang rings, in addition to the presence of amorphous eosinophilic material within a tumor stroma consisting of well-vascularized loose



FIGURE 2. Occlusal view of superior teeth showing the generalized character of the gingival overgrowth.

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FIGURE 3. Lingual view of the region in which the Pindborg's Tumor was removed. The larger nodular mass between the first and second molars can be observed.

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fibrous connective tissue, which formed the basis of a mononuclear inflammatory infiltrate (Figs 4-6). The lesion was lined with orthokeratinized or hyperparakeratinized stratified pavementous epithelium of the oral mucosa, which showed foci of acanthosis, hydropic degeneration, spongiosis, and some large oral filiform projections at a right angle to the direction of the connective tissue. Based on these findings, the diagnosis of CEOT was made. The patient is currently being followed up and shows no signs of recurrence.

Discussion

CEOT is defined by the World Health Organization as a benign tumor arising from odontogenic epithelium without the participation of ectomesenchyme, which shows an intra- or extraosseous location and corresponds to approximately 1% of all odontogenic tumors. The intraosseous location is the most common one and can even cause local

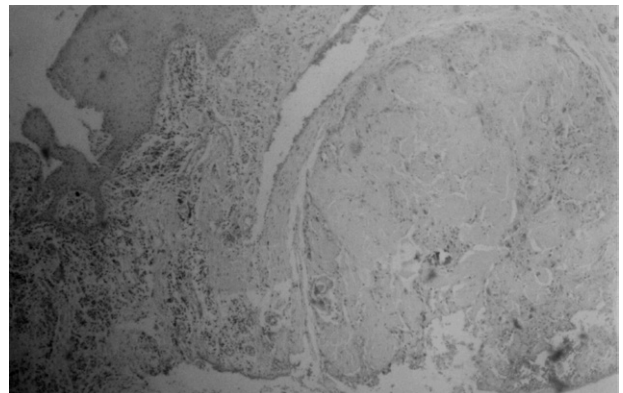


FIGURE 4. A low-power view of the gingival mucosa fragment lined by parakeratinized stratified squamous epithelium present in the lamina propria as irregular strands and nests of epithelial eosinophilic cells and amyloidlike material (hematoxylin-eosin, $\times 40$).

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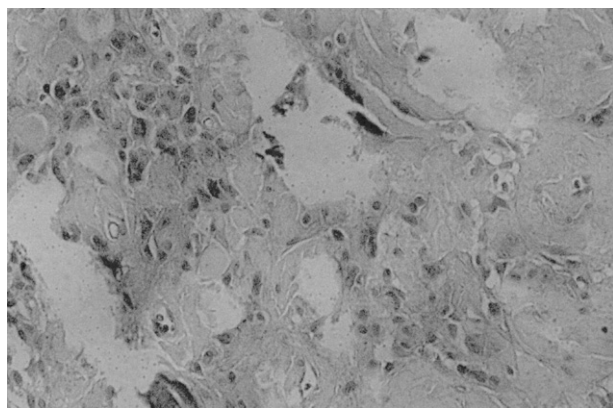


FIGURE 5. Calcifying epithelial odontogenic tumor exhibiting polyhedral epithelial cells with well-defined cellular borders and granular eosinophilic cytoplasm (hematoxylin-eosin, $\times 100$).

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invasion. The peripheral or extraosseous variant is less frequent, accounting for only 6% of CEOT.^{1,8} Only 14 cases of peripheral CEOT have been reported in the scientific literature from its first description by Pindborg in 1996, to 2003. The case described here is quite rare and unusual because of the association of peripheral CEOT with drug-induced gingival growth, a fact not yet reported in the literature.

According to Anavi et al,⁸ some clinical differences exist between central and peripheral CEOTs because the peripheral form is more frequently observed in young patients with a mean age of 34 years, whereas central tumors predominate in adults with a mean age of 44 years. Peripheral CEOTs more frequently affect the region of the premolars (71%) and are generally small (1.2 to 3 cm) and indolent, although Ching et al⁹ reported a case of extraosseous CEOT with progressive invasion towards the maxillary sinus. In contrast, central CEOTs are more often located in the posterior region of the maxilla (64%). According to Bouckaert et al,⁴ the biological behavior of these tumors, although benign and of slow growth, can be locally aggressive, with the authors reporting a case of central CEOT invading the maxillary and ethmoidal sinus with intracranial extension, causing compression and brain abscess.

In fact, of the 14 cases of peripheral CEOT reported thus far, 7 were detected in women and 6 in men, while in 1 case the gender was not specified. Age ranged from 12 to 64 years, with a peak incidence in the third decade of life, and a mean age of 34 years. Eight of these cases were located in the mandibular gingiva and 6 in the maxillary gingiva (Table 1). The present case differs in some aspects from those reported in the literature because the

lesion was observed in an 18-year-old male patient. However, with respect to location, ie, the mandibular gingiva, the present case was similar to most reported cases.

The histogenesis of peripheral CEOTs is uncertain, but it has been suggested that the lesion arises from remnants of the dental lamina or from basal cells of the oral epithelium.⁵ Bouckaert et al⁴ reported that these tumors probably originate from oral epithelium.

Clinically, peripheral CEOT manifests as a small well-circumscribed mass of slow growth, which is generally sessile and asymptomatic but can cause pain in some cases.^{6,7} In the present case, an association with drug-induced gingival growth was observed, but the lesion was sessile and located in the region of the lower right first molar, showing a color similar to that of the mucosa and without defined limits between the lesion and the drug-induced gingival growth, thus being clinically confused with pyogenic granuloma.

The histopathological spectrum of CEOT includes nests, islets, or masses of polyhedral epithelial cells containing eosinophilic cytoplasm and a hyperpigmented nucleus, with intercellular bridges being observed.^{1,8,17} Other characteristics include variable amounts of amyloid material and calcifications, some showing concentric arrangements called Liesegang rings. Philipsen and Reichart¹ suggested that despite histochemical, immunohistochemical, and ultrastructural studies, the nature of the amyloid material is unknown and poorly understood. In contrast, Yamaguchi et al¹⁸ proposed that this material probably has a β -protein conformation

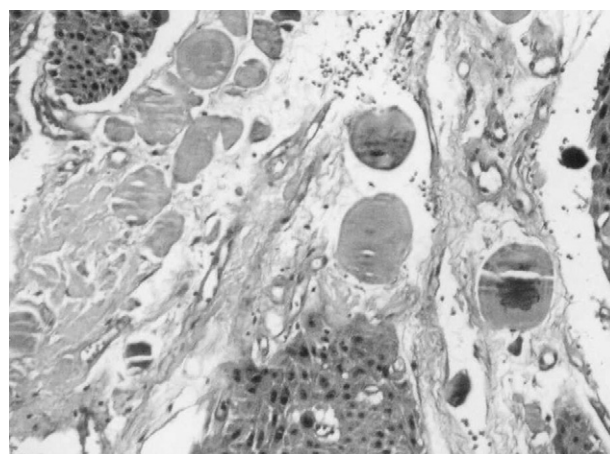


FIGURE 6. Microphotography showing hyperpigmented epithelial cells arranged in chains. Liesegang rings and foci of basophilic material resembling dystrophic calcifications can be observed (hematoxylin-eosin, $\times 100$).

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Table 1. CASES OF EXTRAOSSEOUS OR PERIPHERAL CALCIFYING EPITHELIAL ODONTOGENIC TUMOR (CEOT) REPORTED IN THE LITERATURE (N = 14)

Reference	Age (Years)	Gender	Located in Gingival Area
Pindborg (1966) ¹⁰	29	F	22
Pindborg (1966) ¹⁰	16	F	41, 42
Decker and Laffite (1967) ¹¹	40	M	Mandible, premolar
Abrams and Howell (1967) ¹²	16	F	41, 42
Patterson et al (1967) ¹³	12	M	41 or 31
Krolls and Pindborg (1974) ¹⁴	60	nd	Anterior mandible
Wertheimer et al (1977) ¹⁵	20	M	22-24
Ai-Ru et al (1982) ¹⁶	32	F	34-36
Ai-Ru et al (1982) ¹⁶	47	F	43, 44
Takeda et al (1983) ⁵	31	F	16, 17
Houston and Fowler (1997) ³	64	M	24
Houston and Fowler (1997) ³	27	M	44, 45
Ching et al (2000) ⁹	23	M	Left maxilla
Mesquita et al (2003) ⁶	48	F	13

Abbreviations: F, female; M, male; nd, not determined.

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similar to the enamel matrix. Mesquita et al⁶ showed that the deposits of amyloid-like material consist of extracellular matrix proteins such as fibronectin and collagens I and III despite their different labeling intensity compared with nonamyloid extracellular matrix, a fact that led the authors to conclude that this material in CEOTs represents nonamyloid deposits in which the different groups of the reported proteins correspond to extracellular matrix components.

Clear cells have also been observed in some CEOTs as shown by Kumamoto et al¹⁹ and Mesquita et al.⁶ These cells are generally characterized by a vacuolated cytoplasm rich in glycogen and periodic-acid Schiff-positive material. When the lesion predominantly consists of clear cells, it might be confused with salivary gland tumors such as oncocytoma and mucoepidermoid carcinoma, in addition to metastatic renal carcinomas, clear cell odontogenic carcinomas, and peripheral ameloblastomas.^{3,20}

In agreement with Bouckaert et al,⁴ the morphological findings of peripheral CEOT led us to infer that this lesion arises from the oral epithelium because the cells of these tumors often resemble squamous cells. In the present case, the morphological characteristics observed left no doubt that the lesion was a peripheral CEOT because we observed proliferation of hyperpigmented epithelial cells arranged in islets and chains, foci of basophilic material resembling dystrophic calcifications, some of them showing concentric arrangements characteristic of Liesegang rings, in addition to the presence of amorphous eosinophilic material and the absence of radiographic signs.

Various lesions that occur in the gingiva can be confused with peripheral CEOT, including fibrous hyperplasia, pyogenic granuloma, peripheral giant cell lesion, and peripheral ossifying fibroma.^{6,21} In the present case, the clinical hypothesis for the general clinical presentation was drug-induced gingival growth based on the fact that the patient had reported the use of drugs for the treatment of epilepsy inducing this condition and had been submitted to gingivoplasty in other regions where the histopathological exam showed morphological findings compatible with drug-induced gingival hyperplasia. However, the diagnostic hypothesis for the lesion located in the lower right first molar was pyogenic granuloma. The association between peripheral CEOT and drug-induced gingival growth is still uncertain; however, its association with lesions of odontogenic origin has already been reported, eg, the adenomatoid odontogenic tumor that was reported by Damm et al.²¹

Although some investigators have raised the hypothesis that CEOT shows the same biological behavior as ameloblastoma, experience indicates that the former is less aggressive.²² Thus, the treatment of choice for this lesion has varied among authors, ranging from simple enucleation and curettage to block resection with safety margins. According to Junqueira et al,²³ conservative treatment (enucleation and curettage) has shown a recurrence rate of 14%, while no relapse is observed when the treatment is aggressive (block resection with safety margins). The choice of therapeutic conduct can be based on the size of the tumor, with small lesions being removed by simple enucleation, whereas in the case of larger lesions, a radical or more aggres-

sive conduct may yield a better prognosis. In agreement with the latter authors, the treatment of choice in the present case was simple enucleation, in view of the clinical diagnosis.

The description and discussion of rare lesions such as peripheral CEOT is of the utmost importance because these case reports permit the determination of the frequency and behavior of these entities and better treatment. We report here for the first time a rare case of peripheral CEOT associated with drug-induced gingival growth.

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